TACE-mediated ectodomain shedding of the type I TGF-beta receptor downregulates TGF-beta signaling.

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Public Summary:

Scientific Abstract:
Regulating TGF-beta receptor presentation provides an avenue to alter a cell's responsiveness to TGF-beta. We report that activation of the Erk MAP kinase pathway decreases the TGF-beta-induced Smad3 activation due to decreased cell surface levels of the type I receptor TbetaRI, but not the type II receptor. Inhibition of TACE activity or expression enhanced the cell surface TbetaRI levels and TGF-beta-induced Smad3 and Akt activation. Accordingly, silencing TACE expression in cancer cells enhanced the TbetaRI presentation and TGF-beta responsiveness, including the antiproliferative effect of TGF-beta, and epithelial-to-mesenchymal transition. These results establish a mechanism for downregulating TGF-beta signaling through TACE activation by the Erk MAP kinase pathway and a strategy for evasion of tumor suppression and modulation of epithelial-to-mesenchymal transition during cancer progression. The decreased growth inhibition by TGF-beta, due to elevated TACE activity, complements the growth stimulation resulting from increased release of TGF-alpha family ligands.